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EXAMINER	
COUNTS, GARY W	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,602	PATRICELLI, MATTHEW	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-32 and 48-74* is/are pending in the application.

4a) Of the above claim(s) *61-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-32,48-59 and 74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The Request for Continued Examination and the amendment filed 04/26/05 is acknowledged and has been entered.

Election/Restrictions

I. Claims 21-32, 48-59 and 74, drawn to methods of determining the presence, amount, or activity of one or more active target proteins in a complex protein mixture, classified in class 435, subclass 7.9.

II. Claims 60-73, drawn to a method of comparing the presence, amount or activity of one or more active target proteins in each of two or more discrete proteomes, classified in class 435, subclass 973.

1. Inventions I and II are independent and distinct inventions. Invention II requires two or more discrete proteomes and also involves contacting each of the discrete proteomes with a single activity bases probe and also involves the step of comparing the presence, amount or activity of the active target proteins in each of the discrete proteomes and Invention I does not require these limitations.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and the search required for one group is not required for other restriction for examination purposes as indicated is proper.

2. During a telephone conversation with Michael Hay, Applicant Representative on 06/16/05 a provisional election was made with traverse to prosecute the invention of

Group I, claims 21-32, 48-59 and 74. Affirmation of this election must be made by applicant in replying to this Office action. Claims 60-73 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 21-28, 30-32, 48-54, 56-59 and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (US 2002/0076739) in view of Cravatt et al (US 2002/0045194).

Aebersold et al disclose affinity tagged reagents (chemical probe) for use in methods of determining target protein abundance between proteomes (complex protein mixtures). Aebersold et al discloses that these chemical probes bind to specific sites of

target proteins (p. 2, paragraph 0017). Aebersold et al disclose contacting the complex protein mixture with the chemical probes (p. 7, col 1, lines 1-14). Aebersold et al disclose digesting the proteins in the sample mixture with proteolyzing agents (p. 7, paragraph 0070). Aebersold et al disclose separating the affinity tagged peptides by affinity isolation procedures (p. 7, paragraph 0071). Aebersold et al disclose analyzing the isolated-tagged peptides (those containing the probe) by liquid chromatography-mass spectrometry or capillary electrophoresis-mass spectrometry (p. 7, paragraph 0072). Aebersold et al disclose the removal of excess affinity tagged reagent (probe) prior to the step of digestion (p. 7, paragraph 0069). Aebersold et al disclose the use of internal standards in the method (p 6).

Aebersold et al differ from the instant invention in failing to teach the probe is an activity based probe and the use of a single activity based probe.

Cravatt et al disclose probes that have specificity to the active form of proteins (abstract). Cravatt et al disclose that these probes provides for methods for the measurement of specific active proteins in a proteome (p. 12, paragraphs 0116-0018). Cravatt et al disclose that the probe may contain a fluorescent moiety (p. 11, para. 0110). Cravatt et al disclose the use of antibodies to capture ligands comprising a fluorescent moiety (p. 9, paragraph 0095). Cravatt et al teach measurement of the active proteins in single and combined samples. Cravatt et al specifically teach that a single activity based probe can be used in the methods (p. 12, paragraph 0118). Cravatt et al disclose that these activity based probes provide for methods of measuring protein activity in proteomics, as opposed to protein abundance (paragraph 0005).

Cravatt et al disclose that active target proteins such as enzymes are key to almost every biologic process and that current preteomic approaches are limited to abundance of active target proteins and that this is a key limitation because the activity of enzymes is often regulated by post-translational modification (paragraph 0005).

It would have been obvious to one of ordinary skill in the art to substitute the activity based probe such as taught by Cravatt et al for the probe of Aebersold et al because Cravatt et al teaches the use of a single probe in single and combined samples and also because Cravatt et al recognized the need for methods of measuring protein activity in proteomics, as opposed to protein abundance (taught by Aebersold et al). Further, Cravatt et al discloses that active target proteins such as enzymes are key to almost every biologic process and that current preteomic approaches are limited to abundance of active target proteins and that this is a key limitation because the activity of enzymes is often regulated by post-translational modification. Therefore, a skilled artisan can have a reasonable expectation of success in incorporating an activity based probe taught by Cravatt et al in the method of Aebersold et al.

With respect to the recitation "specifically binds predominantly to a single target site" as recited in the instant claims. Cravatt et al disclose that the activity based probes are comprised of the formula R*(F-L)-X (para 0083) and discloses a list of ligands X which are used in the formula (para. 0095). This activity based probe is the same as the activity based probe disclosed by applicant on page 15, paragraph 0049 of the specification and contains the same ligands (see pages 16-17, paragraph 0055 of the

specification). Therefore, the activity based probe of Cravatt et al would specifically bind predominantly to a single target site.

6. Claims 29 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al and Cravatt et al in view of Little et al (Us 2003/0003465).
See above for teachings of Aebersold et al and Cravatt et al.

Aebersold et al and Cravatt et al differ from the instant invention in failing to teach prior to the proteolyzing step, the one or more active target protein bound to the probe are bound to a solid support.

Little et al disclose immobilizing a target polypeptide (protein) to a solid support. Little et al disclose that the target polypeptide (protein) can be immobilized by a streptavidin or avidin to biotin interactions (p. 9, paragraph 073). Little et al disclose that the immobilization of a target polypeptide (protein) provides a means to isolate the polypeptide, as well as a means to manipulate the isolated target polypetide prior to mass spectrometry (p. 3, lines 1-6). Little et al disclose that the term polypeptide and protein are interchangeable (p. 5, paragraph 0045).

It would have been obvious to one of ordinary skill in the art to immobilize the active target protein complex of Aebersold and Cravatt et al to a solid support prior to the proteolysing step because Little et al teaches that the immobilization of a target polypeptide (protein) provides a means to isolate the polypeptide, as well as a means to manipulate the isolated target polypetide prior to mass spectrometry. Further, Aebersold et al teaches isolating the bound complex from excess probe prior to the

proteolyzing step. Therefore a skilled artisan would have a reasonable expectation of success immobilizing the active target protein complex prior to a proteolyzing step.

Response to Arguments

7. Applicant's arguments filed April 26, 2005 have been fully considered but they are not persuasive.

Note: Applicant's arguments directed toward claims 60-73 are moot because they are directed to a non-elected invention and are withdrawn from consideration.

Applicant's arguments of the 103 rejection of Aebersold in view of Cravatt.

Applicant argues that the methods according to Aebersold teach away from the present invention because Aebersold does not teach an activity based probe that binds predominantly to one site, multiple peptides are produced creating a substantially more complex mixture than is initially provided. Examiner agrees that Aebersold does not teach an activity based probe that binds predominantly to one site. However, Applicant's arguments are not found persuasive because the combination of Aebersold et al and Cravatt et al teach an activity based probe that binds predominantly to one site and thus would create a simplified complex mixture.

Applicant argues that Aebersold does not disclose or suggest a method as recited in the instant claims. Applicant states as acknowledged by the Examiner, "Aebersold et al differ from the instant invention in failing to teach the probe is an activity based probe." Applicant states that this is a very significant difference. Activity based probes

label a single target site on each protein, thus, following a proteolytic digest, only a single labeled peptide from each protein will be present. Prior to the present invention, the standard belief in the mass spectrometry community was that a single peptide did not provide data with sufficient confidence to unambiguously identify a protein through automated sequence searching. This is not found persuasive because the motivation to combine the references comes from the teachings as stated above because Cravatt et al teaches the use of a single probe in single and combined samples and also because Cravatt et al recognized the need for methods of measuring protein activity in proteomics, as opposed to protein abundance (taught by Aebersold et al). Further, Cravatt et al discloses that active target proteins such as enzymes are key to almost every biologic process and that current preteomic approaches are limited to abundance of active target proteins and that this is a key limitation because the activity of enzymes is often regulated by post-translational modification. Further, as stated by Applicant on page 18 of the Remarks section filed April 26, 2005. The activity based probes of the present invention (which are the same probes as Cravatt (see above rejections)) are larger than the Aebersold probes and the labeling sites of the probes result in very large peptides allowing for mass spectrometry data. Therefore, one of ordinary skill in the art would expect the combination of Aebersold and Cravatt to provide data to identify a protein.

Applicant argues that the probes described by Aebersold teach away from the present invention, as the probes label multiple sites on each target protein. Thus when a labeled sample according to Aebersold is digested, the number of labeled peptide

species is substantially increased, typically at least 10X versus the number of labeled proteins. This is not found persuasive because the applicant is arguing the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant further argues that because the methods of the present invention produce substantially fewer peptides, this allows for separation methods not applicable or possible with the Aebersold methods, e.g., lower resolution, high throughput separation methods such as CE or LC (instead of LCMS/MS typically used for the Aebersold methods). In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., methods, e.g., lower resolution, higher throughput separation methods such as CE or LC) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, since the combination of Aebersold and Cravatt teach a single activity based probe the methods would produce fewer peptides. Therefore, absent evidence to the contrary the combination of Aebersold and Cravatt would produce substantially fewer peptides and allow for separation methods such as discussed above.

Applicant argues that specific labeling sites of activity based probes can be accurately predicted in most cases, thus the peptides potentially present in a digested,

ABP-labeled sample can also be analyzed in silico (computationally). Even within families of closely related enzyme, peptides derived from tryptic digest of ABP labeled proteins have significant differences in their amino acid sequences enabling separation by standard chromatographic methods, and/or identification by mass spectrometry. Generally>95% of such peptides are non-redundant, i.e., the particular sequence is not shared by any other protein. This is neither taught or suggested by the cited prior art, and is a key realization for the success and/or general functionality of the claimed method. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., ABP-labeled sample can also be analyzed in silico (computationally) or Generally>95% of such peptides are non-redundant, i.e., the particular sequence is not shared by any other protein) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that at the time of the present invention, the ability to obtain consistent proteolytic digest in a multitude of proteomic mixtures had not been described or validated in the art. Nearly all published proteolytic digest procedures suggested using an amount of protease (trypsin) equal to a particular fraction of the amount of protein in the sample. This is not found persuasive because it is unclear what Applicant is arguing. There is nothing in the claims that require obtaining consist

proteolytic digestion in a multitude of proteomic mixtures nor is there any requirements for trypsin in the claims.

Applicants arguments of the combination of Little with the primary references

Applicant argues that reliance on Little is unable to cure the deficiencies of the primary reference and no motivation to combine the cited reference is provided in the Office Action. Applicant further states that the combination of references can only be advanced with the improper hindsight analysis.

This is not found persuasive because the Examiner specifically disclosed the motivation to combine the references because Little et al teaches that the immobilization of a target polypeptide (protein) provides a means to isolate the polypeptide, as well as a means to manipulate the isolated target polypetide prior to mass spectrometry. Further, Aebersold et al teaches isolating the bound complex from excess probe prior to the proteolyzing step. Therefore a skilled artisan would have a reasonable expectation of success immobilizing the active target protein complex prior to a proteolyzing step. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary Counts
Examiner
Art Unit 1641
June 23, 2005

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06/23/05